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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/069,999	03/01/2002	Takashi Kawasuji	2002_0288A	5732

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EXAMINER	
EPPERSON, JON D	

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 10/17/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/069,999	KAWASUJI ET AL.	
	Examiner	Art Unit	
	Jon D. Epperson	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 July 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) *1-6 and 15-23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7-9* is/are rejected.

7)☒ Claim(s) *9-14* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/14,9/15,3/26,3/1*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

1. Receipt is acknowledged of a Response to a Restriction Requirement, which was dated on July 12, 2005.

Status of the Claims

2. Claims 1-23 are pending.

3. Applicant's response to the Restriction and/or Election of Species requirements is acknowledged (Applicant elected ***without traverse*** Group II, claims 7-15) and claims 1-6 and 16-23 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim (see below i.e., ***Response to Restriction and/or Election of Species***).

4. Please note: Applicant's elected species (Compound No. H-3 in Table 35 on page 124) was searched and was not found in the prior art. Thus, the search was expanded to non-elected species, which *were* found in the prior art, see rejections below. Also, see MPEP § 803.02 (emphasis added):

> On the other hand, should no prior art be found that anticipates or renders obvious the elected species, the search of the Markush-type claim will be extended. If prior art is then found that anticipates or renders obvious the Markush-type claim with respect to a nonelected species, the Markush-type claim shall be rejected and claims to the nonelected species held withdrawn from further consideration. ***The prior art search, however, will not be extended unnecessarily to cover all nonelected species.*** Should applicant, in response to this rejection of the Markush-type claim, overcome the rejection, as by amending the Markush-type claim to exclude the species anticipated or rendered obvious by the prior art, the amended Markush-type claim will be reexamined. The prior art search will be extended to the extent necessary to determine patentability of the Markush-type claim. In the event prior art is found during the reexamination that anticipates or renders obvious the amended Markush-type claim, the claim will be rejected and the action

made final. Amendments submitted after the final rejection further restricting the scope of the claim may be denied entry.

5. Claim 15 is withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected species (see below i.e., ***Response to Restriction and/or Election of Species***).

6. Therefore, claims 7-14 are examined on the merits in this action.

Response to Restriction and/or Election of Species

7. Applicant's election of Group II (claims 7-15) is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a) and/ or 37 CFR 1.111(b)).

8. Applicant's election of species is also acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election of species has also been treated as an election without traverse (MPEP § 818.03(a) and/ or 37 CFR 1.111(b)).

9. As a result, the restriction requirement and/or election of species is still deemed proper and is therefore made FINAL.

Information Disclosure Statement

10. The information disclosure statement filed March 1, 2002, fails, in part, to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because two publications cited therein, marked AA and AB, lack inventor names, a necessary element for consideration of U.S. Patent References. While the other patent and other publications cited therein, and supplied, therewith, have been considered as to the merits, these two publications have not. Applicant is advised that the date of any re-submission of these citations contained in this information disclosure statement or the submission of the missing element – their publication dates – will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPE § 609 C(1).

11. The references listed on applicant's PTO-1449 form have been considered by the Examiner. A copy of the form is attached to this Office Action (e.g., 9/14/05, 9/15/04, 3/26/02 and 3/1/02).

Specification

12. The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Objections to the Claims

13. Claims 9-14 are objected to because of the following informalities:

A. Claim 9 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form or rewrite the claim(s) in independent form. Claim 9 depends alternatively from claim 8. Claim 8 recites in part: "Y is optionally substituted heteroaryl." However, claim 9 recites the limitation "Y is $-C(=R^2)-R^3-R^4$ ... ." Claim 9, therefore, does not further limit claim 8 because "$-C(R^2)R^3-R^4$" does not represent a "heteroaryl" group.

B. Claims 10-14 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from any other multiple dependent claim. See MPEP § 608.01(n). Accordingly, the claims 10-14 have not been further treated on the merits.

Claims Rejections - 35 U.S.C. 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

14. Claims 8 and 9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. For **claim 8**, the phrase "the heteroaryl has a bond at an atom adjacent to a heteroatom in Y" is vague and indefinite. For example, it is not clear when a heteroaryl wouldn't have a bond at an atom adjacent to a heteroatom in the ring (i.e., heteroaryl

groups always have this feature such as, for example, heteroatom-bond-second ring atom-bond-third ring atom-bond, etc. wherein the underlined bonds are at the second ring atom which is adjacent to the heteroatom)? Thus, it is not clear how this limitation further limits and/or defines the claimed subject matter. Applicants are requested to clarify and/or correct. Therefore, claims 8 and all dependent claims are rejected under 35 U.S.C. 112, second paragraph.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

15. Claims 7-9 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Applicants' claims are directed to a broad genus of compounds of the formula (I) including "... a prodrug thereof" (e.g., see claim 7). Applicants further define a prodrug, in part, as "... a derivative of the compound of the present invention ... having a group which can be decomposed ... metabolically, and such prodrug is converted to a pharmaceutically active compound of the present invention by means of ... placing the compound *in vivo* under a physiological condition" (e.g., specification, page 29, lines 8-12). Thus, Applicants' claims encompass virtually an infinite number of compounds as

no limitations are placed on the structure of the prodrugs, the disease state with which the prodrugs are associated, and the animal host and/or metabolic pathway that would otherwise be required to degrade said prodrugs *in vivo*.

In contrast, Applicants' specification does not even provide a single working example (or species) of a prodrug that can be metabolically decomposed *in vivo* (i.e., no metabolic pathways are disclosed). Applicants' specification only lists "potential" species for prodrugs that can be chemically decomposed using simple hydrolysis/solvolysis techniques (e.g., see specification, pages 29-30).

To satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the claimed invention (e.g., see *In re Edwards*, 568 F.2d 1349, 1351-52, 196 USPQ 465, 467 (CCPA 1978); see also see also *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111 (CAFC 1991)). The "written description" requirement may be satisfied by using "such descriptive means as words, structures, figures, diagrams formulas, etc., that fully set forth the claimed invention" (e.g., see *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966). In the present case, Applicants' specification does not describe a single species of prodrug that can be metabolically degraded (see above). In addition, when there is *substantial variation within the genus*, one must describe a sufficient variety of species to reflect the variation within the genus (e.g., see MPEP § 2163.05). Here, the variation within the genus would be enormous because the nature of the claimed compounds would depend on a vast number of undefined biological systems (which would be required to decompose the claimed prodrugs) that do not share common attributes (e.g., Silverman,

page 500, paragraph 1, "The prodrug to drug conversion can occur before absorption, during absorption, after absorption, or at a specific site in the body [i.e., shows great variability in mechanism of action]"). In addition, the nature of the prodrug would vary depending on the purpose for which said prodrug was designed and/or discovered (e.g., see page Silverman, page 499 wherein prodrugs are designed for aqueous solubility, absorption, site specificity, instability, prolonged release, toxicity, poor patient acceptability, etc.).

The CAFC has also stated that a "written description on an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." (e.g., see *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1405 (1997), quoting *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993)). Here, Applicants have failed to provide a definition, structure, formula or chemical name for any of the compounds that fall within the scope of a prodrug that can be metabolically degraded. In addition, the CAFC has stated that a genus, which is set forth only in functional terms, "... is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function" (e.g., see *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (1997)). Here, Applicants claim prodrugs that can only be distinguished from other compounds by their function (i.e., their ability to undergo metabolic degradation), which was held to be impermissible in *Lilly*. Just as the generic term "cDNA" did not provide an adequate written description for the broad class of mammalian or vertebrate

insulin DNA in *Lilly*, neither does the generic term "prodrug" provide an adequate written description for the broad class of formula (I) prodrugs because the term "prodrug" only defines what the compound does (i.e., it ability to be metabolized) rather than what the compound is (e.g., a chemical formula). Furthermore, describing the product (i.e., formula (I)) that is obtained from the prodrug upon metabolic degradation does not provide a written description of the drug prodrug itself. This position is consistent with *Lilly* where the CAFC held that the disclosed protein product (i.e., insulin) did not provide an adequate written description for the DNA encoding that product. In fact, this case is even more egregious than *Lilly* because there is no "genetic code" to correlate the prodrug with the metabolized product.

Thus, applicants have not demonstrated in "full, clear, concise, and exact terms" that they are in possession of the claimed invention especially with regard to prodrugs that undergo complex metabolic degradation (as opposed to simple hydrolysis/solvolysis, see below). Furthermore, the general knowledge and level of skill in the art do not supplement the omitted description because no known structure/function relationship and/or chemical properties exists that could otherwise be used to show possession of the claimed prodrugs especially with regard to complex and/or unknown metabolic interactions (e.g., see Silverman, page 500, paragraph 2, "Some prodrugs are not designed as such, the biotransformations are fortuitous, and it is discovered only after isolation and testing of the metabolites that activation of the drug had occurred [no such isolation and testing has been disclosed in the specification]"; see also page 500, last paragraph, "When designing a prodrug, you should keep in mind that a particular

metabolic transformation may be species specific. Therefore, a prodrug whose design was based on rat metabolism studies may not necessarily be effective in humans [i.e., there is no correlation going from one species to another]"; see also page 500, "... a bioprecursor prodrug contains a different structure that cannot be converted into the active drug by simple cleavage [i.e., hydrolysis/solvolysis] of a group from the prodrug [i.e., there is no structure/function relationship for these types of metabolic transformations]"). In addition, no generally accepted method for producing these unknown compounds has been set forth. It is well settled that claiming only a result (e.g., ability to act as a prodrug) fails to satisfy the constitutional requisite of promoting the progress of science and the useful arts since this seeks to monopolize all possible ways to achieve a given result, far beyond those means actually discovered or contemplated by the inventor, so that others would have no incentive thereafter to explore a field already fully dominated. *O'Reilly v. Morse*, 15 How. 62, *In re Fuetterer*, 50 CCPA 1453, 1963 C.D. 620, 795 O.G. 783, 319 F.2d 259, 138 USPQ 217 ; *Siegel v. Watson*, 105 U.S. Appl. D.C. 344, 1959 C.D. 107, 742 O.G 863, 267 F.2d 621, 121 USPQ 119.

Claims Rejections - 35 U.S.C. 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

16. Claim 7 is rejected under 35 U.S.C. 102(b) as being anticipated by Thomson et al. (WO 99/06410) (Date of Publication is **February 11, 1999**) (of record).

For ***claim 7***, Thomson et al. (see entire document) disclose methyl 3-(4-benzyl-thien-3-yl)-2-(tert-butoxycarbonylamino)acrylate (e.g., see Thomson et al, page 138, lines 1-2, Example 38, step b), which anticipates the claimed invention. For example, methyl 3-(4-benzyl-thien-3-yl)-2-(tert-butoxycarbonylamino)acrylate falls within the scope of Applicants' claimed formula (I) when Z = hydrogen, X = *tert*-butoxycarbonylamino (i.e., an optionally substituted amino), Y = $-C(=R^2)-R^3-R^4$ wherein R^2 and R^3 = oxygen and R^4 is a methyl group (i.e., an optionally substituted alkyl), A = thiophene (i.e., an optionally substituted aromatic heterocycle), Z^1 = bond, Z^3 = bond, Z^2 = methylene (i.e., an alkylene) and R^1 = phenyl (i.e., an optionally substituted aryl group). In addition, the -C(Z)-C(X)Y portion of the molecule substitutes at an atom adjacent to the S hetero atom in the ring and p = 1.

17. Claims 7-9 are rejected under 35 U.S.C. 102(b) as being anticipated by Ogura et al. (EP 9 913 392 A1) (Date of Publication is **May 6, 1999**) as evidenced by Applicants' specification (e.g., see specification, 29-30, especially, page 30, first full paragraph).

For ***claims 7-9***, Ogura et al. (see entire document) disclose, for example, compound II-144 (e.g., see Ogura et al., Table 16, page 295, line 19), which anticipates the claimed invention. For example, II-144 falls within the scope of Applicants' claimed formula (I) when Z = CN (i.e., optionally substituted alkyl), X = hydroxy (i.e., the *tert*-butyl acyloxy "prodrug" of the hydroxyl group, -O-C(=O)-(*tert*-Bu)); see also Applicants' specification, pages 29 and 30, especially page 30, line 10 wherein the -O-

C(=O)-(*tert*-Bu) group is defined as a "particularly preferred" acyloxy prodrug for a hydroxyl group), Y = pyridyl, A = thiazole (i.e., an optionally substituted aromatic heterocycle), Z^1 = bond, Z^3 = bond, Z^2 = -NR^{10}- wherein R^{10} = hydrogen, and R^1 = phenyl (i.e., an optionally substituted aryl). In addition, the -C(Z)-C(X)Y portion of the molecule substitutes at an atom adjacent to the "N" hetero atom in the A ring and p = 1. Furthermore, the -O-C(=O)-O-(*tert*-Bu) group at the X position inherently represents a prodrug of the hydroxyl group as exemplified by Applicants' specification, which would be expected to undergo simple hydrolysis/solvolysis (e.g., see specification, pages 29-30, especially page 30, first full paragraph, "When the compound of the formula (I) has a hydroxyl group, an acyloxy derivative ... is exemplified as a prodrug"; see also page 30, line 10). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference. See *In re Best,* 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (571) 272-0808. The examiner can normally be reached Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jon D. Epperson, Ph.D.
October 4, 2005